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primarily squamous-cell carcinomas (Harrison & Heath, 1986). [The Working Group noted that concurrent untreated controls and groups treated with cadmium metal only were not available.]

Groups of male Wistar Crl:[WI]BR rats, 22 weeks old, were given a single intraperitoneal injection of 18 mg/kg bw NDMA followed 4 h and four days later by intramuscular injections of cadmium chloride into the thigh (total doses of cadmium, 1.5 mg/kg bw [20 rats] or 3.0 mg/kg bw [30 rats]) or no further treatment (20 rats). Two other groups of 20 rats were given cadmium alone, and a group of five untreated rats served as controls. The animals were observed for 52 weeks. Cadmium chloride alone was not acutely lethal; NDMA alone caused 5% mortality, low-dose cadmium plus NDMA induced 10% mortality and high-dose cadmium plus NDMA induced 30% mortality. All treatments markedly reduced body weight [extent not stated] within one week of exposure, but by the end of the experiment the weights were similar to those of untreated controls. Only rats surviving to week 30 were included in the tumour analysis. Cadmium chloride increased ($p \leq 0.05$, Fisher exact test) the incidence of renal tumours induced by NDMA (NDMA alone, 2/18 rats examined; NDMA plus low-dose cadmium chloride, 10/18; NDMA plus high-dose cadmium chloride, 11/21) but did not induce significant numbers when given alone (low-dose, 1/20; high-dose, 0/20). Cadmium chloride also increased the incidence of hepatocellular adenoma (NDMA alone, 1/18; NDMA plus pooled cadmium chloride groups, 9/39). In a second experiment, 30 rats (same strain, six weeks old) were given intramuscular injections of cadmium as cadmium chloride at a dose of 1 mg/kg bw into the thigh on days 0, 4, 5 and 6 and of 2 mg/kg bw on day 12; one day later, the animals received an intraperitoneal injection of 18 mg/kg bw NDMA. Further groups received NDMA alone (20 rats), cadmium chloride alone (20 rats) or remained untreated (four rats). Survival and body weights were similar in all groups. Cadmium chloride increased ($p \leq 0.05$, Fisher exact test) the incidence of NDMA-induced renal tumours (NDMA alone, 2/19; NDMA plus cadmium chloride, 15/26) but did not induce any renal tumours when given alone (0/20). The incidences of hepatocellular adenomas were: NDMA alone, 3/19; NDMA plus cadmium chloride, 0/26; cadmium chloride alone, 1/20 (Wade *et al.*, 1987).

4. Other Relevant Data

The extensive literature on cadmium has been reviewed (Friberg *et al.*, 1985, 1986b; Nordberg & Nordberg, 1988; Nordberg *et al.*, 1992; US Occupational Safety and Health Administration, 1992; WHO, 1992b). The following summary comprises illustrative studies only.

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Cadmium may enter the body by ingestion, inhalation and, to a very limited extent, by passage through the skin, but few studies have examined fractional absorption of cadmium in humans. In one study, rice was cultured in a nutrient solution containing cadmium-115

[compound unspecified] and then cooked and administered to a healthy male subject. Whole-body counting for three days and counting in faeces and urine suggested that 5% of the cadmium had been absorbed. When cadmium-115 was administered in an acid solution [presumably on an empty stomach], the absorption was almost 30% (Yamagata *et al.*, 1975). In another study, faecal elimination of cadmium-115 was detected up to 20–30 days after oral intake of the tracer as the chloride, probably reflecting sloughing of mucosal cells containing cadmium; the remaining whole-body retention averaged 4.6% (McLellan *et al.*, 1978). A higher absorption rate has been seen in women, in whom fractional absorption of ^{115}Cd-cadmium chloride was correlated inversely with serum ferritin concentration (Flanagan *et al.*, 1978).

The extent of deposition in the lungs depends on particle size and shape, ventilatory parameters and airway geometry. The fact that smokers have higher cadmium levels in the body shows that cadmium is absorbed in the lungs (see section 1.3.9). In a study of autopsy specimens, lower pulmonary concentrations of cadmium were observed in ex-smokers than in smokers. A half-time for pulmonary cadmium of 9.4 years was calculated from these data (Paäkkö *et al.*, 1989).

Low excretion rates of cadmium lead to efficient retention in the body. Analysis of cadmium in autopsied organs shows that most of the body burden is retained in the kidneys and liver. The biological half-time in kidneys was estimated to be 12–20 years (Elinder *et al.*, 1976; Tsuchiya *et al.*, 1976; Kjellström & Nordberg, 1978; Roels *et al.*, 1981; WHO, 1992b) and that in the liver somewhat shorter (Tsuchiya *et al.*, 1976; Kjellström & Nordberg, 1978). Neutron activation analysis has been used to determine cadmium concentrations in liver and kidney of cadmium-exposed workers *in vivo*. In workers without kidney dysfunction, the cadmium concentrations in the two organs correlated well, and both correlated well with urinary cadmium excretion (Roels *et al.*, 1981). As also reflected in other studies (Lauwerys *et al.*, 1980), urinary cadmium excretion can be regarded as a measure of the body burden of this metal in individuals with normal kidney function. In 64 active and retired smelter workers without kidney dysfunction, urinary excretion of metallothionein also correlated well with the cadmium burdens of liver and kidneys (Shaikh *et al.*, 1990). In workers with cadmium-induced kidney dysfunction, urinary cadmium excretion is higher, and kidney burdens tend to decrease relative to the concentrations in the liver (Roels *et al.*, 1981).

The concentration of cadmium in the blood depends mainly on recent absorption of the metal and tends to stabilize within a few months after a change in exposure (Lauwerys *et al.*, 1980). The concentrations of cadmium in blood were measured over more than 10 years in five workers in a copper–cadmium alloy factory who had had high exposures to cadmium in the past. The data fitted a two-compartment model, with a first mean half-time of 75–128 days and a second of 7.4–16 years. Two workers with proteinuria had shorter half-times than workers without kidney dysfunction (Järup *et al.*, 1983).

Urinary excretion of absorbed cadmium is the major route of elimination, but it is also excreted in the bile (Friberg *et al.*, 1986b). In an autopsy study of deceased smelter workers, increased lung concentrations of cadmium were found. High concentrations were related particularly to tobacco smoking (Gerhardsson *et al.*, 1986).

Cadmium concentrations in the prostate (50–500 ng/g wet weight) were < 1% of those found in the kidneys (8000–39 000 ng/g wet weight) in five men aged 61–76 years, but within

the prostate the concentrations varied considerably, with the highest concentrations at the base (Lindegaard *et al.*, 1990).

A placental barrier seems to exist: at delivery, cadmium concentrations in umbilical cord blood were about half of those occurring in maternal blood, and cadmium concentrations in human placenta reached a level about 10-fold higher than that seen in maternal blood (Hubermont *et al.*, 1978). Placental transfer was also demonstrated in more recent studies (Kuhnert *et al.*, 1982, 1987).

4.1.2 *Experimental systems*

In mice given ordinary food pellets, average fractional absorption of a single dose of cadmium chloride was 0.2% of non-toxic doses; five to eight times higher absorption rates were recorded in mice on a semisynthetic diet resembling human food (Andersen *et al.*, 1992).

In a study of male Wistar rats exposed by inhalation to cadmium aerosols (see pp. 164, 166–167), the cadmium concentrations in lung tissue homogenate and lung cytosol supernatant were about twice as high for cadmium oxide as for cadmium chloride, both at the end of the 30-day exposure period and two months later. Exposure to a cadmium sulfide aerosol (a combination of sulfide and sulfate) at a 10-fold higher level (1 mg/m^3) resulted in cytosol cadmium concentrations similar to those caused by administration of cadmium oxide at 0.1 mg/m^3. The amount of absorbed cadmium that was retained in the liver and kidneys was higher if delivered as cadmium oxide than if given as cadmium chloride at the same concentration (Glaser *et al.*, 1986).

In a study of Long–Evans and Fischer 344 rats exposed to aerosols of cadmium chloride, oxide dust and sulfide dust, pulmonary retention of cadmium chloride and sulfide (half-time, 85 days and 11–76 days, respectively) was similar, whereas that of cadmium oxide dust was somewhat longer (half-time, 217 days). In contrast, there was no transfer to the kidney or liver of cadmium administered as cadmium sulfide, but the levels in faeces were high. Monkeys (*Macaca fascicularis*) did not accumulate cadmium in the kidney after inhaling cadmium sulfide dust but did so after inhaling cadmium oxide (Oberdörster & Cox, 1989).

A low-molecular-weight protein, metallothionein, occurs mainly in liver and kidney and binds cadmium. Its synthesis is induced by cadmium and other divalent metals. Metallothionein-bound cadmium released from the liver is cleared by glomerular filtration and taken up by the renal tubules (Nordberg *et al.*, 1971; Nordberg, 1972). Metallothionein production in the intestinal mucosa was induced by oral administration of zinc to Wistar rats. Subsequent oral administration of cadmium increased the retention of cadmium in the kidneys but decreased retention in the liver in comparison with non-pretreated rats (Min *et al.*, 1991). Induced mallothionein production was not detectable in rat ventral prostate, and cadmium in these cells seems to bind to other (non-inducible) proteins. In male Wistar rats, subcutaneous injection of cadmium stimulated expression of the metallothionein-I gene in the liver and the dorsal prostate, while gene expression in the ventral prostate remained unchanged (Waalkes *et al.*, 1992a,b).

Zinc deficiency may affect tissue deposition of cadmium. In male Wistar rats given a diet low in zinc (7 ppm) for nine weeks with different levels of cadmium for the last six weeks, retention of cadmium was enhanced in liver, kidney and testis, with concomitant, marked